REVIEW

Nutritional Metabolomics and the Classification of Dietary Biomarker Candidates: A Critical Review

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ABSTRACT

Recent advances in metabolomics allow for more objective assessment of contemporary food exposures, which have been proposed as an alternative or complement to self-reporting of food intake. However, the quality of evidence supporting the utility of dietary biomarkers as valid measures of habitual intake of foods or complex dietary patterns in diverse populations has not been systematically evaluated. We reviewed nutritional metabolomics studies reporting metabolites associated with specific foods or food groups; evaluated the interstudy repeatability of dietary biomarker candidates; and reported study design, metabolomic approach, analytical technique(s), and type of biofluid analyzed. A comprehensive literature search of 5 databases (PubMed, EMBASE, Web of Science, BIOSIS, and CINAHL) was conducted from inception through December 2020. This review included 244 studies, 169 (69%) of which were interventional studies (9 of these were replicated in free-living participants) and 151 (62%) of which measured the metabolomic profile of serum and/or plasma. Food-based metabolites identified in ≥1 study and/or biofluid were associated with 11 food-specific categories or dietary patterns: *1*) fruits; *2*) vegetables; *3*) high-fiber foods (grain-rich); *4*) meats; *5*) seafood; *6*) pulses, legumes, and nuts; *7*) alcohol; *8*) caffeinated beverages, teas, and cocoas; *9*) dairy and soya; *10*) sweet and sugary foods; and *11*) complex dietary patterns and other foods. We conclude that 69 metabolites represent good candidate biomarkers of food intake. Quantitative measurement of these metabolites will advance our understanding of the relation between diet and chronic disease risk and support evidence-based dietary guidelines for global health. *Adv Nutr* 2021;12:2333–2357.

Keywords: metabolomics, dietary biomarkers, nutrition, omics, food exposures

Introduction

Diet plays an important role in modulating the risk of chronic diseases, including obesity, diabetes, cardiovascular disease, and certain cancers (1). Food intake in epidemiological studies has traditionally been assessed using self-reported and often memory-based approaches, including 24-h dietary recalls, weighted food diaries, or FFQs. The reliability and validity of these tools have been questioned due to the presence of potentially serious systematic and random measurement errors (2, 3). Errors such as misreporting of total energy intake and food portion sizes by 30–88% (4, 5) have hindered efforts to disentangle diet–disease relations. During the past decade, metabolomics has emerged as a valuable tool for revealing changes in metabolic profiles induced by recent or long-term/habitual diets (6, 7). High-throughput platforms for metabolomics enable comprehensive characterization of low-molecular-weight metabolites in biological samples, and they offer a complement (or, in some cases, an alternative) to self-report tools for objective assessment of "true" food exposures. Metabolomic studies may also better characterize dose–response relations, which would be an advance over FFQs because FFQs generally offer sufficient precision only to distinguish high from low consumers of food and food groups varying considerably across populations (8).

The primary focus of nutritional metabolomics has been the discovery of specific metabolites associated with food consumption and its impact on chronic disease risk. Such studies have led to the discovery of atherogenic trimethylamine *N*-oxide (TMAO), a metabolite produced by the gut microbiome from dietary nutrients such as choline, betaine, and L-carnitine that are prevalent in eggs, red meat, and fish (9, 10). The ability to discriminate metabolites of foods in a robust and generalizable manner depends on intrinsic factors such as characteristics of the study population (e.g.,

genetics, ethnicity, food habits) and extrinsic factors such as quantity and duration of food exposure. This problem is further exacerbated because there is no clear consensus on the choice of optimal study designs, sample size, metabolomic approach, biospecimen type, and methods used for metabolite identification and quantification (11).

The two main analytical techniques used in metabolomics are MS and NMR; the latter method is highly robust, requires minimal sample handling, but is less sensitive. In contrast, MS-based approaches are usually preceded by more extensive sample preparation and chromatographic separations based on LC, GC, or capillary electrophoresis for broader metabolome coverage with improved selectivity, including isomer resolution (12, 13). Recent advances in high-resolution MS, particularly the implementation of standardized LC-MS methods, have made it possible to detect thousands of molecular features when performing nontargeted metabolomics for hypothesis generation; however, rigorous data-filtering approaches are needed to identify and authenticate metabolites while reducing data set redundancy and artifact signals to prevent false discoveries (8, 14, 15). On the other hand, targeted metabolomics is also widely used to quantify a specified list of known metabolites for hypothesis testing using validated analytical methods. Alternatively, both targeted and nontargeted strategies using more than a single analytical platform are increasingly used in large-scale metabolomic studies depending on sample volume requirements, sample throughput, and operational costs.

There are several thousand low-molecular-weight compounds derived from foods. The Food Biomarker Alliance is a joint initiative across 11 countries aimed at discovery and validation of dietary biomarkers (http://foodmetabolome.org/foodball). The Food Database (FooDB) (https://foodb.ca) is the most comprehensive database with >70,000 metabolites derived from foods and food constituents (16). Also, Exposome-Explorer (http://exposome-explorer.iarc.fr) is a manually curated database of exposome chemicals including dietary and pollutant biomarkers (17). Although these databases are comprehensive and useful, it is challenging for the scientific community to critically appraise and classify robust dietary biomarkers in a rapidly evolving field. Furthermore, recent nutritional metabolomic reviews do not distinguish between health/disease states of participants, and thus disease status may confound the association between dietary intake and their biomarkers (18, 19).

The purpose of this review is to *1*) to generate a comprehensive list of metabolites associated with individual food and food groups in apparently healthy individuals; *2*) report on the study designs, metabolomic approaches, and biospecimen used; and *3*) rate the evidence based on the interstudy repeatability and study design.

Methods

A comprehensive literature search was developed in collaboration with an information scientist. We searched MEDLINE through OVID, EMBASE, Web of Science, BIOSIS, and CINAHL and included published articles from inception until December 2020. We used a comprehensive search strategy including a combination of medical subject heading terms and keywords related to study design, population, individual foods and food groups, and metabolomics. For the details of our search strategy, see **Supplemental Methods**. References of the included studies were manually searched to identify any further relevant studies. Search results from all databases were merged, and duplicates were removed with the use of EndNote citation manager (version X9; Thomson Reuters). Articles were initially screened based on title and/or abstract, and full text of potential articles was retrieved and evaluated independently by 2 reviewers (TR and SMA). Any disagreement was resolved through discussion, and if necessary, a third investigator (RJdS) made the final decision.

Eligibility criteria

Studies were eligible to be included in our review if they *1*) were conducted in healthy adults or children of any sex or ethnicity; *2*) used nontargeted or targeted approaches to identify metabolites of individual foods (e.g., oranges or red meat), complex dietary patterns (e.g., Mediterranean diet or meat-based diet), and/or specific nutrients or nonnutrients (e.g., *trans* fats or carotenoids); and *3*) examined the relation (observational studies) or the effect (intervention studies) of food on metabolites primarily in serum, plasma, or urine samples. We restricted the results to individual foods and food groups but excluded dietary supplements, given that we were interested in reporting metabolites derived from food intake. We excluded studies *1*) that had examined food intake in conjunction with other interventions or lifestyle changes such as weight loss to ensure that a biomarker is specific to food and not some other intervention, *2*) without a control group, and *3*) that enrolled participants with existing disease to ensure that identified biomarkers

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Supplemental Tables 1 and 2, Supplemental Figure 1, and Supplemental Methods are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Address correspondence to RJdS (e-mail: desouzrj@mcmaster.ca).
Abbreviations used: ADD, Average Danish Diet; BFI, biomarker of food intake; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanproponante; DASH, Dietary Approaches to Stop Hypertension Trial; DHPPA, 3-(3,5-dihyroxyphenyl)-1-propanoic acid; HEI, Healthy Eating Index; NND, New Nordic Diet; TMAO, trimethylamine *N*-oxide.

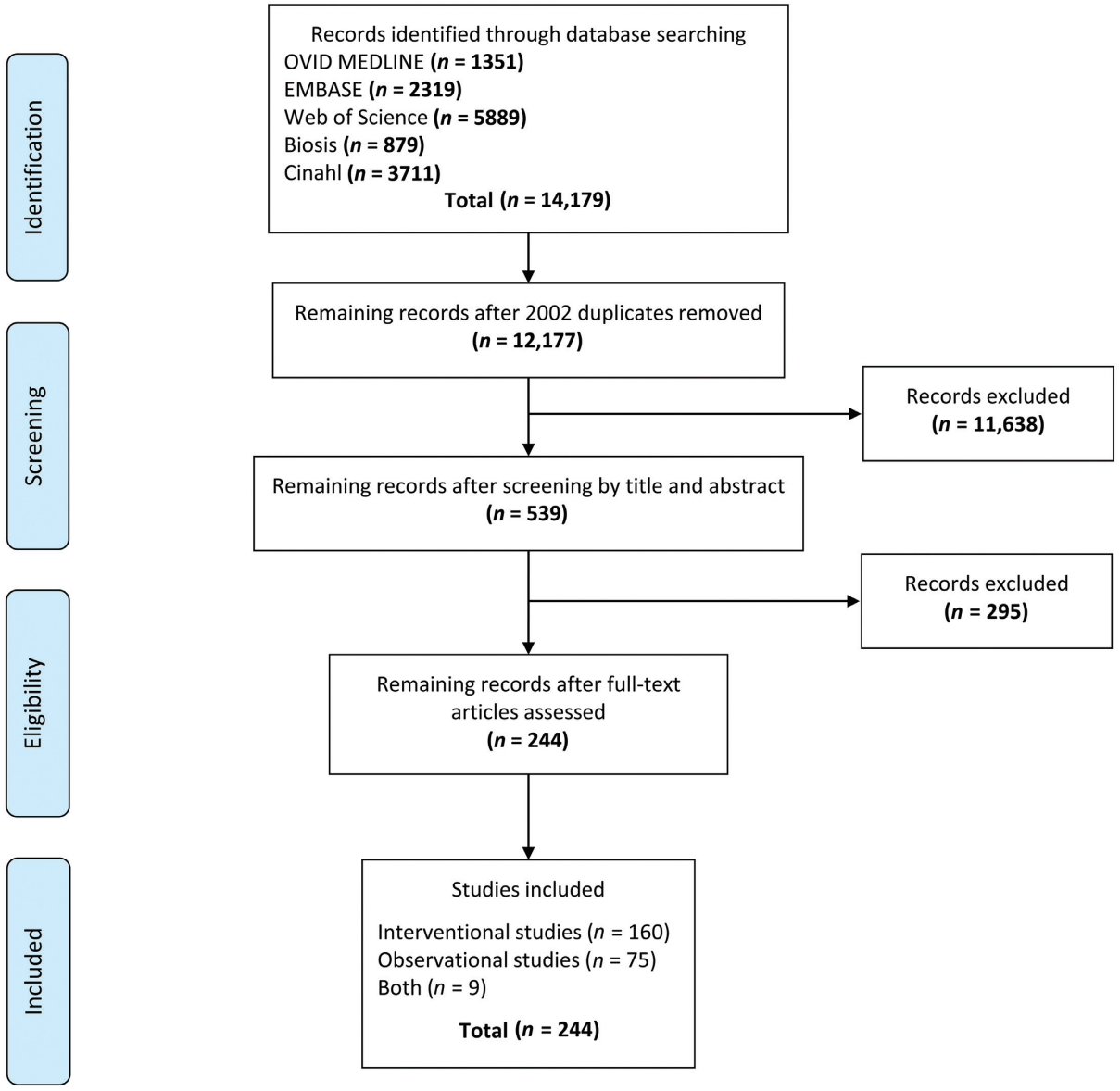

FIGURE 1 PRISMA flow diagram of the literature search process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

are not a result of a pathologic process or pharmacological intervention.

Study selection criteria

We identified 14,179 records across the 5 databases, and 12,177 remained after removal of duplicates (**Figure 1**). The number of potentially relevant studies narrowed to 539 after title and abstract screening. After full-text review, a total of 244 studies remained eligible and were included in this systematic review.

Data extraction and analysis

We extracted information regarding publication details, including name of first author and year of publication, and study characteristics, including age, country, type of study (e.g., feeding study or cross-sectional study), sample size, length of follow-up, specification of analytical technique, biological sample (urine or blood), exposure and/or comparator details, method of dietary assessment (only for observational studies), and all resulting metabolites following diet exposure (**Supplemental Tables 1** and **2**). Given the large number and chemical diversity of food metabolites, a data-reduction approach was applied in which only those metabolites that were identified in $\geq$2 different studies and/or biofluids (blood and urine) are presented and discussed in this review.

Assessing level of evidence

We developed a scoring system to rate the evidence for each metabolite as a candidate biomarker of food intake into 1 of 3

mutually exclusive categories: good, fair, or poor. The rating is based on empirical evidence of interstudy repeatability and study design.

Repeatability

Metabolites identified in >1 study were assigned a score of 2 points for each of these studies that was an interventional study plus 1 additional point for each observational study. Only metabolites that were replicated were assigned a score. The following algorithms were used to assess replication:

- Two independent publications: A metabolite identified by 1 observational study and 1 interventional study was assigned a total score of 3 points (1 × 1 point for observational study and 1 × 2 points for interventional study).
- A single publication reporting results from 2 independent cohorts/studies of a metabolite of a food, and both were congruent, was assigned a score of 3 points (1 × 1 point for observational study and 1 × 2 points for interventional study).
- Two different biological fluids for the same cohort (urine and blood): For example, a biomarker identified in both urine and blood sample was assigned a score of 2 points if identified in an observational study (1 × 1 [urine] + 1 × 1 [blood]) and a score of 4 points if identified in an interventional study (1 × 2 [urine] + 1 × 2 [blood]).

Thus, the lowest score for a replicated metabolite was 2 points, classified as poor evidence; a score of 3–4 was considered as fair evidence, and a score of ≥5 points was considered good evidence (**Table 1**). Although this scoring system has not been published previously in the literature, we have carefully designed it to be a tool for assessing the extent of evidence of metabolites as related to recent or habitual food consumption. Certain metabolites recently recognized in the scientific community as "strong" biomarkers of food intake (BFIs), such as proline betaine for citrus fruits, were also correctly classified as good using our scoring system.

Results

This review included 244 studies, 169 (69%) of which were interventional studies (9 of these were replicated in free-living participants) and 101 (41%) of which measured the metabolomic profile of urine, plasma (n = 64), serum (n = 46), or both plasma/serum and urine samples (n = 41). A total of 7273 individuals contributed data to 169 interventional studies (average of 42 participants per study), and 79,256 individuals participated in 84 observational studies (average of 922 participants per study). Most studies focused on the adult population, with only 2 intervention and 7 observational studies including children and/or adolescents. All but 2 intervention and 3 observational studies did not provide information on age of participants, and nearly all studies reported sex-related information. The dietary biomarkers were measured in blood (plasma or serum) and/or urine sample and were detected using LC-MS (mainly with either reversed-phase or hydrophilic interaction modes), GC-MS, ^{1}H-NMR, or other analytical methods (e.g., flow-injection electrospray ionization–MS, capillary electrophoresis–MS, or inductively coupled plasma MS) (**Supplemental Figure 1**). Each metabolite was scored based on the interstudy repeatability and study design score system described previously. As expected, proline betaine was classified to have good evidence (score >5) for intake of citrus fruits because it appeared in 2 interventional studies (score = 4) and 5 observational studies (score = 5), for a combined score of 9. Meanwhile, ergothioneine for intake of mushrooms appeared in 2 observational studies and was classified to have poor evidence (score = 2). Overall, our review concluded that 69 metabolites are good, 161 are fair, and 48 are poor biomarkers of foods.

Most food-derived exogenous compounds are biotransformed into ≥1 metabolites following primary and secondary metabolism and have an optimal detection window within a 24-h period depending on dose and frequency of food intake (mostly with urine sample), although some extend to ≥48 h. In this section, we discuss robust dietary biomarkers associated with intake of specific foods or complex dietary patterns. Metabolites identified in >1 study or biofluid were grouped into the following 11 categories: *1*) fruits; *2*) vegetables; *3*) high-fiber (grain-rich); *4*) meats; *5*) seafood; *6*) pulses, legumes, and nuts; *7*) alcohol; *8*) caffeinated beverages, teas, and cocoas; *9*) dairy and soya; *10*) sweet and sugary foods; and *11*) complex dietary patterns and other foods.

Fruits

A total of 29 subcategories of fruits were identified in this systematic review, of which 9 categories had reported ≥1 metabolite that was replicated (Table 1, **Figure 2**A). Metabolites for intake of fruits were analyzed in 2 interventional (20, 21) and 8 observational studies (22–29), fruit juices in 1 interventional study (20) and 3 observational studies (22, 30, 31), citrus fruits in 3 interventional (20, 32, 33) and 6 observational studies (22, 27, 31, 34–36), orange in 3 interventional studies (20, 33, 37) and 1 observational study (22), orange juice in 7 interventional studies (21, 38–43) and 1 observational study (34), apple in 5 interventional (20, 44–47) and 2 observational studies (22, 45), banana in 1 interventional study (48) and 4 observational studies (31, 34, 48, 49), strawberry in 4 interventional studies (50–53), and cranberry juice in 4 interventional studies (54–57). Several studies reported higher concentration of proline betaine with intake of fruits in general (21, 24–26). Proline betaine was also identified as the most frequent biomarker of citrus fruit (20, 22, 27, 31, 32, 34) and orange juice (21, 34, 38, 40), fruit juice (22, 30, 31), and the only metabolomic signature of orange fruit (22, 33, 37). Proline betaine was specific to the habitual consumption of citrus fruit or fruit juice due to its high natural abundance with appreciable amounts found in less commonly eaten foods, such as *Stachys affinis* or Chinese artichoke (58). In addition,

TABLE 1 List and scoring of food metabolites replicated in the literature[1]

	Score		
Food name	**Good (≥5)**	**Fair (3–4)**	**Poor (2)**
Fruits	Proline betaine (5)[2]	Hippuric acid (4)[2]	
Strawberry	Pelargonidin glucuronide (6)		
Apple		Epicatechin sulfate (4)	
		Hydroxyphenylvaleric acid sulfate (4)	
		Xylose (3)[2]	
Banana		3-Methoxytyramine sulfate (3)[2]	
		Dopamine sulfate (3)[2]	
		Methoxyeugenol glucuronide (3)[2]	
		Salsolinol sulfate 1 (3)[2]	
Fruit juice		Proline betaine (4)	
		N-methylproline (3)	
		Scyllo-inositol (3)	
Cranberry juice		Ferulic acid sulfate (4)	
		Sinapic acid (4)	
		Quinic acid (4)	
		Hippuric acid (4)	
Orange juice	Proline betaine (7)[2]	3-(3′-Hydroxy-4′-methoxyphenyl)hydracrylic acid (4)	
	Hippuric acid (6)	3-(3′-Hydroxy-4′-methoxyphenyl)propionic acid (4)	
	4′-Hydroxyhippuric acid (6)	3-(4′-Methoxyphenyl)propionic acid-3′-sulfate (4)	
	3′-Hydroxyhippuric acid (6)		
	4-Hydroxyphenylacetic acid (6)		
Orange	Proline betaine (5)[2]		
Citrus fruit	Proline betaine (9)[2]	*N*-methylproline (4)	
		Naringenin (3)[2]	
		Hesperetin (3)[2]	
		Chiro-inositol (3)	
		Scyllo-inositol (3)	
Broccoli	Sulforaphane (8)	Sulforaphane cysteinylglycine (4)	
	Sulforaphane *N*-acetylcysteine (8)	Erucin-cysteine (4)	
	Sulforaphane cysteine (8)	Erucin-*N*-acetylcysteine (4)	
	Isothiocyanates (6)		
Broccoli sprouts	Sulforaphane (8)	Erucin (4)	
Cruciferous vegetables		*S*-Methyl-L-cysteine-sulfoxide (3)[2]	
Green leafy vegetables			CMPF
Mushrooms			Ergothioneine
High-fiber (grain-rich)	Alkylresorcinols (8)	2-Aminophenol sulfate (4)[2]	Daidzein
	3-(3,5-DHPPA (5)[2]	DHBA (3)[2]	Genistein
Whole-grain rye bread		Alkylresorcinols (4)	
		DHPPA sulfate (3)[2]	
Meat	Creatinine (6)[2]	Creatine (5)[2]	
		O-acetyl-L-carnitine (3)[2]	
		4-hydroxyproline (3)[2]	
		Glutamine (3)[2]	
Chicken/poultry	3-Methylhistidine (11)[2]	Anserine (4)[2]	Pyroglutamine[3]
		Carnosine (4)[2]	
		O-acetyl-L-carnitine (3)[2]	
Processed meat	*O*-acetyl-L-carnitine (6)[2]		
Red meat	*O*-acetyl-L-carnitine (6)[2]	TMAO (4)	
		Carnosine (4)[2]	
		Carnitine (3)[2]	
		Anserine (3)[2]	
Seafood	DHA (22:6n–3) (5)	CMPF (3)	Docosapentaenoic acid (22:5n–3)
		Eicosapentaenoic acid (20:5n–3) (3)	
Fatty fish	DHA (22:6n–3) (5)[2]	Eicosapentaenoic acid (20:5n–3) (4)[2]	
Fish	TMAO (19)[2]	1-Methylhistidine (4)	Lysine
	DHA (22:6n–3) (12)[2]	1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (4)	Methionine
	CMPF (7)[2]	Arsenobetaine (4)	Tryptophan
	Creatine (7)[2]	1-Docosahexaenoylglycero-phosphocholine (3)	Tyrosine
	Eicosapentaenoic acid (20:5n–3) (7)[2]	Docosapentaenoic acid (22:5n–3) (3)[2]	
		Acetylcarnitine (3)[2]	
	Dimethylamine (5)[2]		

(*Continued*)

TABLE 1 (*Continued*)

Food name	Score		
	Good (≥5)	Fair (3–4)	Poor (2)
Seafood (lean)		TMAO (4)	
Seafood and plant protein			DHA (22:6n–3)
Shellfish		CMPF (4)	2-Hydroxybutyrate
Pulses/legumes/nuts		Trigonelline (4) 3-Methylhistidine (4) Dimethylglycine (4) Trimethylamine (4) Lysine (4)	
Dry-bean–enriched diet		Trigonelline (4) Pipecolic acid (4) *S*-methylcysteine (4)	
Nuts (mixed)		Tryptophan betaine (4)	4-Vinylphenol sulfate
Peanuts		Tryptophan betaine (3) 4-Vinylphenol sulfate (3)	
Alcohol		4-Androsten-3β-diol disulfate (3) 2-aminobutyrate (3)	α-Hydroxyisovalerate β-Hydroxyisovalerate 5α-Androstan-3β-diol disulfate 2-Hydroxybutyrate 4-Methyl-2-oxopentanoate Pipecolate Docosapentaenoic acid (22:5n–3) Stearidonate (18:4n–3) Piperine Ethyl glucuronide Palmitoleate (16:1n–7) Dihomo-linoleate (20:2n—6) Malate 17β-Diol disulfate 17β-Diol disulfate 1
Liquor		Ethyl glucuronide (4)	
Dealcoholized red wine	Methylgallic sulfate (6) Σ(Epi)catechin glucuronides (6) 3-Hydroxyphenylacetic acid (6) *p*-Coumaric acid (6)	Ethylgallate sulfate (4) Ethylgallate (glucuronide 1) (4) Ethylgallate (glucuronide 2) (4) ΣMethyl(epi)catechin glucuronides (4) ΣDihydroxyphenyl-γ-valerolactone glucuronide (4) ΣDihydroxyphenyl-γ-valerolactone sulfates (4) ΣMethoxy-hydroxyphenyl-γ-valerolactone glucuronide (4) 2,4-Dihydroxybenzoic acid (4) 2,6-Dihydroxybenzoic acid (4) 2,5-Dihydroxybenzoic acid (4) 3,5-Dihydroxybenzoic acid (4) 4-Hydroxybenzoic acid (4) 3-Hydroxybenzoic acid (4) Gallic acid (4) Methylgallic acid (4) 2-Hydroxyphenylacetic acid (4) Caffeic acid (4) Ferulic acid (4) 3-(3-Hydroxyphenyl) propionic acid (4) Enterolactone (4) Pyrogallol (4) Syringic acid (4) Ethylgallate (4) 3,4-Dihydroxyphenylacetic acid (4) Dihydrocaffeic acid (4) (Epi)catechin sulfates (4) Enterolactone (4)	

(*Continued*)

TABLE 1 (*Continued*)

Food name	Score		
	Good (≥5)	Fair (3–4)	Poor (2)
Wine		Ethyl glucuronide (3)	2,3-Dihydroxyisovalerate 2,3-Butanediol *Scyllo*-inositol
Red wine	ΣMethyl(epi)catechin glucuronides (6) Methylgallic acid sulfate (5)[2]	Gallic acid (4) Methylgallic acid (4) 3-Hydroxyphenylacetic acid (4) *p*-Coumaric acid (4) (Epi)catechin glucuronide (4) DHPV (4) DHPV 2 (4) ΣDHPV glucuronides (4) Ethylgallate (3)[2]	
Cocoa	3-Methylxanthine (7)[2] 3-Methyluric acid (5)[2] 7-Methylxanthine (5)[2] Theobromine (5)[2]	Epicatechin-glucuronide (4) 5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone glucuronide (3)[2]	
Coffee	Paraxanthine (13)[2] Caffeine (13)[2] 1-Methylxanthine (10)[2] Quinate (9)[2] Theophylline (10)[2] Hippuric acid (9)[2] Trigonelline (9)[2] 5-Acetylamino-6-amino-3-methyluracil (8)[2] Dihydroferulic acid (8) 1,7-Dimethylurate (6)[2] 1,3,7-Trimethylurate (6)[2] 3-Hydroxyhippurate (6)[2] 1,3-Dimethylurate (7)[2] Catechol sulfate (5)[2] Dihydrocaffeic acid (6) Caffeic acid (7)[2] Ferulic acid (5)[2] Feruloylquinic acid (5)[2] Isoferulic acid (6)[2] *N*-(2-furoyl)glycine (5)[2] Theobromine (5)[2]	3-Caffeoylquinic acid (4) 3-Methyl catechol sulfate (4)[2] 3-Methylxanthine (4)[2] 4-Caffeoylquinic acid (4) Dihydrocaffeic acid-3-*O*-sulfate (4) 1-Methylurate (4)[2] 3-Hydroxypyridine sulfate (3)[2] 7-Methylguanine (3)[2] Caffeic acid sulfate (3)[2] Citraconate (3)[2] Cyclo(Leu–Pro) (3) Gallic acid (3)[2] Kynurenic acid (3)[2]	3,7-Dimethyluric acid
Green tea	Hippuric acid (10)	*O*-methyl-epicatechin-*O*-sulfates (4) *O*-me-epigallocatechin-*O*-glucuronide (4) (–)-Epigallocatechin-3-gallate (4)	
Black tea	4-*O*-methylgallic acid (5)[2]	Hippuric acid (4)	
Chocolate	Theobromine (7)[2] 7-Methyluric (5)[2]	7-Methylxanthine (4)[2] 6-AMMU (4) 3,7-Dimethyluric acid (3)[2]	
Dark chocolate		4-Hydroxyphenyl acetate (4)	
Sweet and sugary beverages		Citrulline (3)[2] Taurine (3)[2] Isocitrate (3)[2]	Carbon isotopic signatures (δ^{13}C)
Dairy			Pantothenic acid (vitamin B-5)
Butter		10-Undecenoic acid (11:1n–1) (3)	Pentadecanoate (15:0) Methyl palmitic isomers
Cheese		3-Phenyllactic (4)[2] Proline (4)[2] Methionine (4)[2]	
Milk	Galactonic acid (5)[2]	Galactose (4) Lactose (4) Galactono-1,5-lactone (4) Urea (4)	Uridine

(*Continued*)

TABLE 1 (*Continued*)

Food name	Score		
	Good (≥5)	Fair (3–4)	Poor (2)
High-soy diet	Daidzein (9)[2] Genistein (8)[2] *O*-DMA (5)[2]	Equol (4) Glycitein (3)	Total isoflavonoids
Soy-based drink Soy-based cheese		Pinitol (4) Daidzein (4) Genistein (4)	4-Ethylphenylsulfate
Whey Average Danish Diet		Leucine/isoleucine (4) Theobromine (4) Proline betaine (4)	
DASH diet Fruits and vegetables	Hippuric acid (5)[2]	β-Cryptoxanthin (3)[2] β-Carotene (3)[2] Genistein (3)[2] Total carotenoid (3)[2]	
Healthy Eating Index		CMPF (3)[2] Eicosapentaenoic acid (20:5n–3) (3)[2] Hippuric acid (3)[2]	Docosahexaenoylcholine DHA (22:6n–3) Carotene diol Ergothioneine
High-carotenoid diet		α-Carotene (3)[2] β-Carotene (3)[2] Total carotenoids (3)[2]	
Mediterranean diet New Nordic Diet	TMAO (6)	DHA (22:6n—3) (4)[2] Hippuric acid (4)	CMPF
Vegetarian			Lysine Methionine Tryptophan Tyrosine
Vegan		Alanine (3)[2] Glycine (3)	

[1]Metabolites identified in ≥2 studies. Interstudy repeatability score: interventional studies (2×); observational studies (1×)—example: metabolite found in 2 interventional studies and 1 observational study will have a score of 5. Good = ≥5; fair = 3–4; poor = 2. *m/z* for good metabolites only reported using untargeted analysis: proline betaine for orange (*m/z* = 144.0988); trigonelline (*m/z* = 138.0550), 1,7-dimethylurate (*m/z* = 195.0524), 1,3,7-trimethylurate (*m/z* = 209.068), 3-hydroxyhippurate (*m/z* = 194.0459), 1,3-dimethylurate (*m/z* = 197.0669), and catechol sulfate (*m/z* = 188.9863) for coffee; theobromine for chocolate (*m/z* = 181.0720); and TMAO for NND (*m/z* = 76.0757). CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate; DHBA, 3,5-dihydroxybenzoic acid; DHPPA, 3-(3,5-dihydroxyphenyl)-1-propanoic acid; DHPV, dihydroxyphenyl-γ-valerolactone; NND, New Nordic Diet; *O*-DMA, *O*-desmethylangolensin; TMAO, trimethylamine *N*-oxide; 6-AMMU, 6-amino-5-[*N*-methylformylamino]-1-methyluracil.
[2]Robust biomarker (i.e., reported using both interventional and observational study design).
[3]Inverse association.

studies reported higher level of hippuric acid with intake of fruits (21, 24, 25), orange juice (39, 42, 43), and cranberry juice (55, 56). Other metabolites (including biotransformed hippuric acid metabolites excreted in urine) identified were 3′-hydroxyhippuric acid (39, 42, 43), 4′-hydroxyhippuric acid (41–43), 4-hydroxyphenylacetic acid (39, 41, 43), 3-(3′-hydroxy-4′-methoxyphenyl)hydracrylic acid (41, 42), 3-(3′-hydroxy-4′-methoxyphenyl)propionic acid (42, 43), and 3-(4′-methoxyphenyl)propionic acid-3′-sulfate (41, 43) for orange juice; naringenin (20, 35), hesperetin (20, 35), *N*-methylproline (22, 27, 34), *chiro*-inositol (22, 27), and *scyllo*-inositol (22, 27) for citrus fruits; epicatechin sulfate (45, 47), hydroxyphenyl valeric acid sulfate (47), and xylose (45) for apple; and *N*-methylproline, *chiro*-inositol, and *scyllo*-inositol for intake of fruit juice (22, 30, 31). Pelargonidin, the main anthocyanin highly specific to strawberries, was the only dietary biomarker reported at high concentration after intake of strawberries (50, 51, 53); 3-methoxytyramine sulfate was the only dietary biomarker reported at high concentration after intake of bananas (34, 48); and 1 study reported higher urine and plasma concentration of ferulic acid sulfate and sinapic acid (54), and quinic acid (55, 56) following intake of cranberry juice.

Vegetables

Five of the total 20 vegetable subcategories had identified ≥1 replicated metabolite as a dietary biomarker (Table 1, Figure 2B). Metabolites associated with intake of broccoli were analyzed in 5 interventional studies (59–63), broccoli sprouts in 4 interventional studies (64–67), cruciferous vegetables in 2 interventional (68, 69) and 3 observational studies (22, 27, 34), green leafy vegetables in 3 observational studies (22, 27, 31), and mushrooms in 2 observational studies (31, 34). Studies reported increased concentration of sulforaphane as the frequently identified metabolite, which is derived from hydrolysis of glucosinolates by myrosinase, to be associated with intake of broccoli (62, 63) and broccoli sprouts (64, 65, 67). In addition, sulfur-containing isothiocyanate exogenous compound prevalent in cruciferous vegetables was another more frequently identified metabolite for intake of broccoli

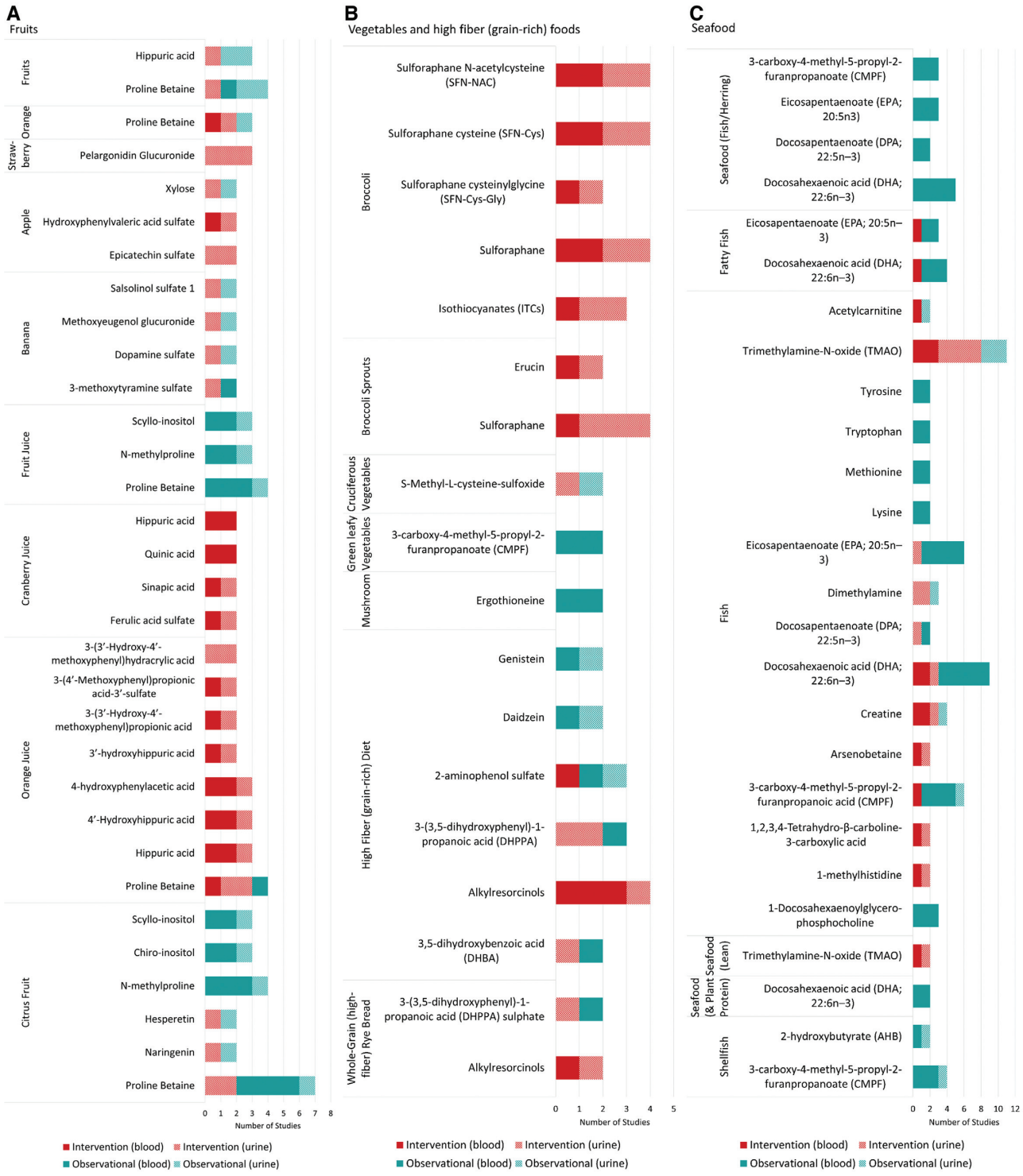

FIGURE 2 Metabolites identified from (A) fruits, (B) vegetables and high-fiber (grain-rich) foods and (C) seafood by number of studies, type of study design, and type of biofluid.

(60, 61), as well as related sulforaphane metabolites/thiol conjugates excreted in urine such as sulforaphane cysteinylglycine (62), sulforaphane cysteine (62, 63), and sulforaphane *N*-acetylcysteine (62, 63). In addition, a higher concentration of erucin was found in urine or blood with intake of broccoli sprouts (65); higher concentrations of erucin-cysteine and erucin *N*-acetylcysteine were found with intake of broccoli (63); and *S*-methyl-L-cysteine-sulfoxide, 3-carboxy-4-methyl-5-propyl-2-furanproponante (CMPF), and ergothioneine were the only metabolites associated with cruciferous

vegetables (34, 69), green leafy vegetables (27, 31), and mushrooms (31, 34), respectively.

High-fiber (grain-rich) foods

The subcategories of high-fiber (grain-rich) foods and whole-grain rye bread had identified ≥1 metabolite that was replicated (Table 1, Figure 2B). Metabolites for a high-fiber diet were examined in 6 interventional (70–75) and 9 observational studies (22, 23, 26, 29, 31, 76–79) and whole-grain rye bread in 7 interventional studies (74, 80–85) and 1 observational study (86). Higher concentrations of urinary and blood alkylresorcinols**,** well-known phenolic lipids that are prevalent in whole-grain wheat and rye, and 3-(3,5-dihyroxyphenyl)-1-propanoic acid (DHPPA), which can be measured as free molecules or as glucuronide or sulfonate conjugates resulting from phase I and II metabolism, were reported with intake of a high-fiber diet (72–75) and whole-grain rye bread (80, 81, 86). Studies reported higher intake of higher dietary fiber to be associated with greater urinary excretion and blood concentration of 3,5-dihydroxybenzoic acid (DHBA) (75, 77), 2-aminophenol sulfate (26, 70, 79), as well as daidzein (23, 76) and genistein (23, 76). The latter 2 phytochemicals are not specific to fiber intake because they are also prevalent in soya products, which have long been associated with habitual dietary patterns and cancer and chronic disease risk (87).

Seafood

Six of the total 8 subcategories had ≥1 metabolite that was replicated (Table 1, Figure 2C). Metabolites for intake of seafood in general were identified in 5 observational studies (13, 26, 30, 31, 88), fatty fish in 1 interventional study (89) and 3 observational studies (90–92), fish in 9 interventional (69, 93–99) and 15 observational studies (22, 24, 27, 31, 34, 52, 88, 90, 94, 99–105), lean seafood in 2 interventional studies (106, 107), seafood in combination with plant protein in 2 observational studies (26, 108), and shellfish in 4 observational studies (22, 27, 34, 105). DHA (22:6n–3), an essential omega-3 fatty acid, was the most frequently reported dietary biomarker of seafood in general (13, 26, 30, 31, 88), fatty fish (89–92), and seafood in combination with plant protein (26, 108). TMAO (a gut microbiota-generated metabolite) was the most frequently reported metabolite associated with intake of fish (52, 69, 94, 97–99, 105). DHA was the second most frequently reported metabolite associated with fish intake (22, 27, 31, 34, 90, 94, 95, 97, 102), and CMPF for seafood in general (26, 30, 31), and shellfish (22, 27, 34). Furthermore, 2 other ω-3 fatty acids, docosapentaenoic acid (22:5n–3) and eicosapentaenoic acid (20:5n–3), were both reported higher after intake of seafood (13, 26, 30, 31) and fish (22, 27, 31, 34, 90, 95), and a higher concentration of eicosapentaenoic acid (20:5n–3) was reported with intake of fatty fish (89–91). Also, elevated levels of CMPF (22, 27, 31, 34, 96), creatine (97, 98, 105), and dimethylamine (69, 99, 105) were associated with intake of fish, and an elevated concentration of TMAO was associated with intake of lean seafood (106, 107). Few other metabolites were replicated for intake of fish. Another metabolite for shellfish was 2-hydroxybutyrate (22), an endogenous metabolite also associated with threonine metabolism and oxidative stress (109). We therefore do not consider it a specific biomarker for shellfish.

Meats

Six meat subcategories were identified in this systematic review, of which 4 categories of overall meat intake, chicken/poultry, processed meat, and red meat had reported ≥1 metabolite that was replicated (Table 1, **Figure 3**A). Examination of potential metabolites for meats was analyzed in 2 interventional (93, 110) and 7 observational studies (24, 31, 90, 101, 104, 111, 112), poultry/chicken in 4 interventional (69, 94, 113, 114) and 6 observational studies (22, 27, 31, 34, 94, 114), processed meat in 1 interventional study (94) and 5 observational studies (22, 27, 31, 94, 115), and red meat in 5 interventional (94, 114, 116–118) and 7 observational studies (22, 27, 34, 94, 114, 115, 119). The most frequently identified metabolites include creatinine (93, 104, 110, 112) for meat, which was first identified a few decades ago and is degraded from creatine during cooking; *O*-acetyl-L-carnitine for red meat (22, 94, 115, 118); and a modified amino acid, 3-methylhistidine, for chicken/poultry (34, 69, 94, 113, 114), which has long been used as a biomarker for muscle protein turnover. Other replicated markers include 4-hydroxyproline (31, 93), glutamine (110, 112), creatine (24, 110, 112), and *O*-acetyl-L-carnitine (104, 110) for meat; TMAO (116), anserine (114), carnosine (94, 114), and L-carnitine (22, 116) specifically for red meat; *O*-acetyl-L-carnitine for processed meat (22, 94, 115); and higher anserine and carnosine (94, 114) and lower pyroglutamine level (27, 31) for chicken/poultry.

Pulses, legumes, and nuts

Four of the 7 subcategories including mixes of pulses, legumes, nuts or dry-bean–enriched diets, mixed nuts, and peanuts had reported ≥1 replicated metabolite (Table 1, Figure 3A). Metabolites for intake of pulses/legumes/nuts in general were analyzed in 3 interventional studies (120–122) and 4 cross-sectional studies (23, 27, 123, 124), dry-bean–enriched diet in 2 interventional studies (125, 126), mixed nuts in 1 interventional study (127) and 3 observational studies (22, 26, 34), and peanuts in 4 observational studies (27, 34, 123, 128). Studies reported higher levels of tryptophan betaine (an indole alkaloid) and 4-vinylphenol sulfate (a xenobiotic associated with benzoate metabolism) with intake of mixed nuts (22, 26, 34) and peanuts (27, 34, 128). In addition, an increased concentration of a vitamin B-3 metabolite, trigonelline, was reported with intake of pulses/legumes/nuts (120) and dry-bean–enriched diet (125, 126). Other dietary biomarkers include 3-methylhistidine, dimethylglycine, trimethylamine, and lysine for pulses/legumes/nuts (120) and pipecolic acid and *S*-methylcysteine for a dry-bean–enriched diet (125, 126).

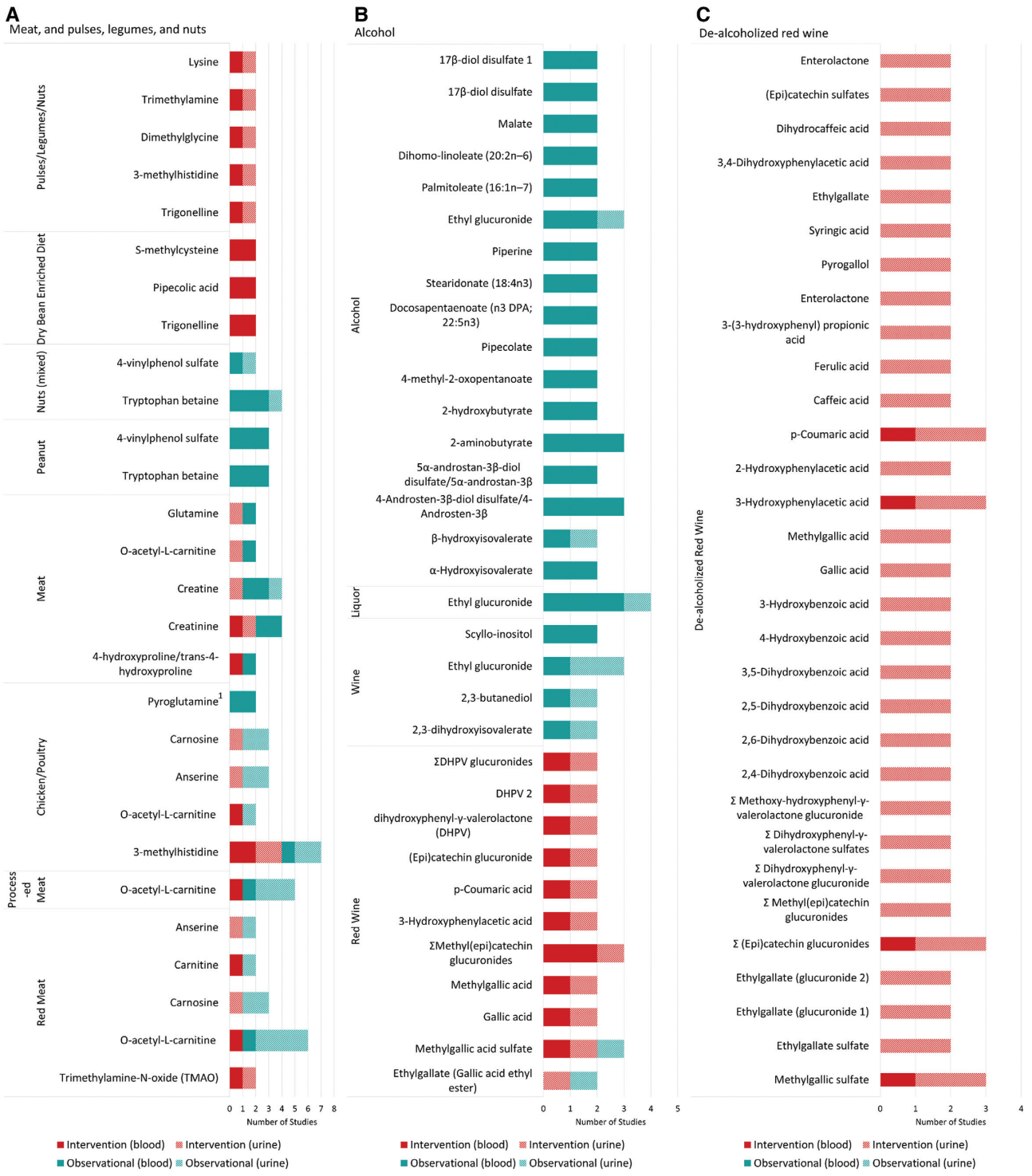

FIGURE 3 Metabolites identified from (A) meats, pulses, legumes, and nuts, (B) alcohol, and (C) dealcoholized red wine by number of studies, type of study design, and type of biofluid. [1]Metabolites in lower concentration compared to control.

Alcohol

The subcategories of alcohol, liquor, wine, red wine, and dealcoholized red wine had reported ≥1 metabolite that was replicated (Table 1, Figure 3B, C). Metabolites for intake of alcohol were analyzed in 12 observational studies (22, 27, 31, 34, 90, 101, 128–133), liquor in 4 observational studies (22, 27, 31, 34), wine in 3 interventional (20, 134, 135) and 6 observational studies (22, 27, 31, 34, 136, 137), red wine in 3 interventional (138–140) and 3 observational studies (34, 36, 136), and dealcoholized red wine in 2 interventional studies (138, 141). Although several metabolomic signatures were identified to be associated with

intake of alcohol, red wine, and dealcoholized red wine, the more frequently reported metabolites include 4-androsten-3β-diol disulfate (27, 31, 128) and 2-aminobutyrate (31, 128, 130) for alcohol; the sum of methyl(epi)catechin glucuronides (138, 140) for red wine; and the sum of (epi)catechin glucuronides, 3-hydroxyphenylacetic acid, and *p*-coumaric acid for dealcoholized red wine (138, 141). Additional metabolites associated with intake of dealcoholized red wine were methylgallic sulfate, 3-hydroxyphenylacetic acid, and *p*-coumaric acid (138). In addition, a higher concentration of ethyl glucuronide, a common secondary metabolite of ethanol excreted in urine, was most frequently reported with intake of wine (22, 34, 137) and liquor (22, 27, 34).

Caffeinated beverages, teas, and cocoas

The subcategories of black tea, green tea, cocoa, and coffee intake had reported ≥1 metabolite that was replicated (Table 1, **Figure 4**A, B). Metabolites for intake of black tea were analyzed in 4 interventional (20, 142–144) and 3 observational studies (31, 145, 146), green tea in 8 interventional studies (143, 144, 147–152) and 1 observational study (146), cocoa in 6 interventional studies (153–158) and 1 observational study (159), and coffee in 10 interventional (20, 46, 160–167) and 16 observational studies (22, 27, 30, 31, 34, 36, 136, 146, 168–175). Paraxanthine (22, 27, 30, 34, 160, 162, 170–172, 174) and 1,3,7-trimethylxanthine (coffee) (22, 30, 34, 160, 162, 169, 171–174) were the most frequently identified markers for coffee intake. Among many, some of the other metabolites more frequently identified for coffee intake include hippuric acid (formed by the conjugation of benzoic acid with glycine) (22, 136, 162, 163, 171, 174) and well-known coffee constituent theobromine and its metabolites 1-methylxanthine (22, 27, 30, 34, 171, 172, 176) and 3-methylxanthine (136, 160, 162, 172). 4-*O*-methylgallic acid, a methyl ether derivative of gallic acid, and hippuric acid were the most frequently identified metabolites for intake of black tea (20, 142, 145) and green tea (143, 144, 147, 148, 152), respectively. Furthermore, higher levels of the well-known coffee constituent theobromine and its metabolite 3-methylxanthine (most frequently) were associated with intake of cocoa (153, 156, 157, 159). There were no biomarkers for decaffeinated coffee that were reported in ≥2 studies, suggesting that the metabolites associated with coffee may likely be metabolites of caffeine and not specific to coffee. 1-Methyluric acid and 5-acetamido-6-amino-3-methyluracil are also widely measured end products of caffeine metabolism prevalent in urine that are associated with caffeinated beverage intake in large populations (172).

Dairy

Three of the 5 subcategories including intake of dairy products, butter, cheese, and milk had reported ≥1 metabolite that was replicated (Table 1, Figure 4A). Metabolites for intake of dairy products were analyzed in 2 interventional studies (177, 178) and 5 observational studies (26, 90, 179–181), butter in 4 observational studies (22, 27, 31, 34), cheese in 3 interventional studies (182–184), and milk in 5 interventional (178, 182–185) and 7 observational studies (23, 27, 29, 34, 180, 181, 186). Galactonic acid (derived from galactose being oxidized via galactono-1,5-lactone) for milk (34, 182, 183) and 10-undecenoic acid (11:1n–1) for butter intake (27, 31, 34) were identified as the most frequently reported dietary biomarkers. A small number of other metabolites were also reported in higher concentrations for these subcategories, including galactose (182, 183), lactose (182, 183), galactono-1,5-lactone (182, 183), uridine (181, 186), and urea for milk (184, 185) and pentadecanoate (15:0) and methyl palmitic acid isomers for butter (27, 31). In addition, studies reported higher concentrations of 3-phenullactic (182, 183), proline (182, 183), and methionine (183, 184) for cheese intake and a higher concentration of pantothenic acid (vitamin B-5) (179, 181) for dairy products.

Sweet and sugary foods

The subcategories of chocolate, dark chocolate, and sweet and sugary beverages had reported ≥1 replicated metabolite (Table 1, Figure 4C). Metabolites for intake of chocolate were analyzed in 2 interventional (33, 52) and 4 observational studies (27, 31, 34, 36), dark chocolate in 2 interventional studies (187, 188), and sweet and sugary beverages in 1 interventional study (189) and 7 observational studies (22, 24, 27, 189–192). Although several metabolomic signatures were associated with intake of chocolate, theobromine (an alkaloid from cocoa plant) (27, 31, 33, 34, 52) followed by its endogenous metabolite 7-methyluric acid (33, 34, 52) were the most frequently reported metabolites. 4-Hydroxyphenyl was the only biomarker reported in higher concentration for intake of dark chocolate (187, 188). Furthermore, citrulline, taurine, isocitrate, carbon isotopic signatures (δ^{13}C) were reported in higher concentration after intake of sweet and sugary beverages (189–191). Various artificial sweeteners can also serve as specific/exogenous biomarkers reflecting intake of low-caloric beverages and processed foods prevalent in a Western diet, including acesulfame K, aspartame, saccharin, sucralose, and steviol glycoside (193).

Complex dietary patterns and other foods

A number of dietary patterns and other food subcategories had identified metabolites that were replicated (Table 1, **Figure 5**A, B). Metabolites for intake of the Average Danish Diet (ADD) were analyzed in 4 interventional studies (33, 194–196), Dietary Approaches to Stop Hypertension (DASH) diet in 1 interventional study (197) and 2 observational studies (108, 198), Healthy Eating Index (HEI) in 1 interventional study (96) and 3 observational studies (26, 108, 198), Mediterranean diet in 3 interventional (199–201) and 5 observational studies (26, 108, 198, 202, 203), New Nordic Diet (NND) in 4 interventional studies (33, 194–196), vegetarian diet in 3 observational studies (100, 104, 204), vegan diet in 1 interventional study (205) and 3 observational studies (100, 104, 112), high carotenoid in 1 interventional study (206) and 1 observational study (207), fruits and vegetables in 4 interventional (69, 208–210) and

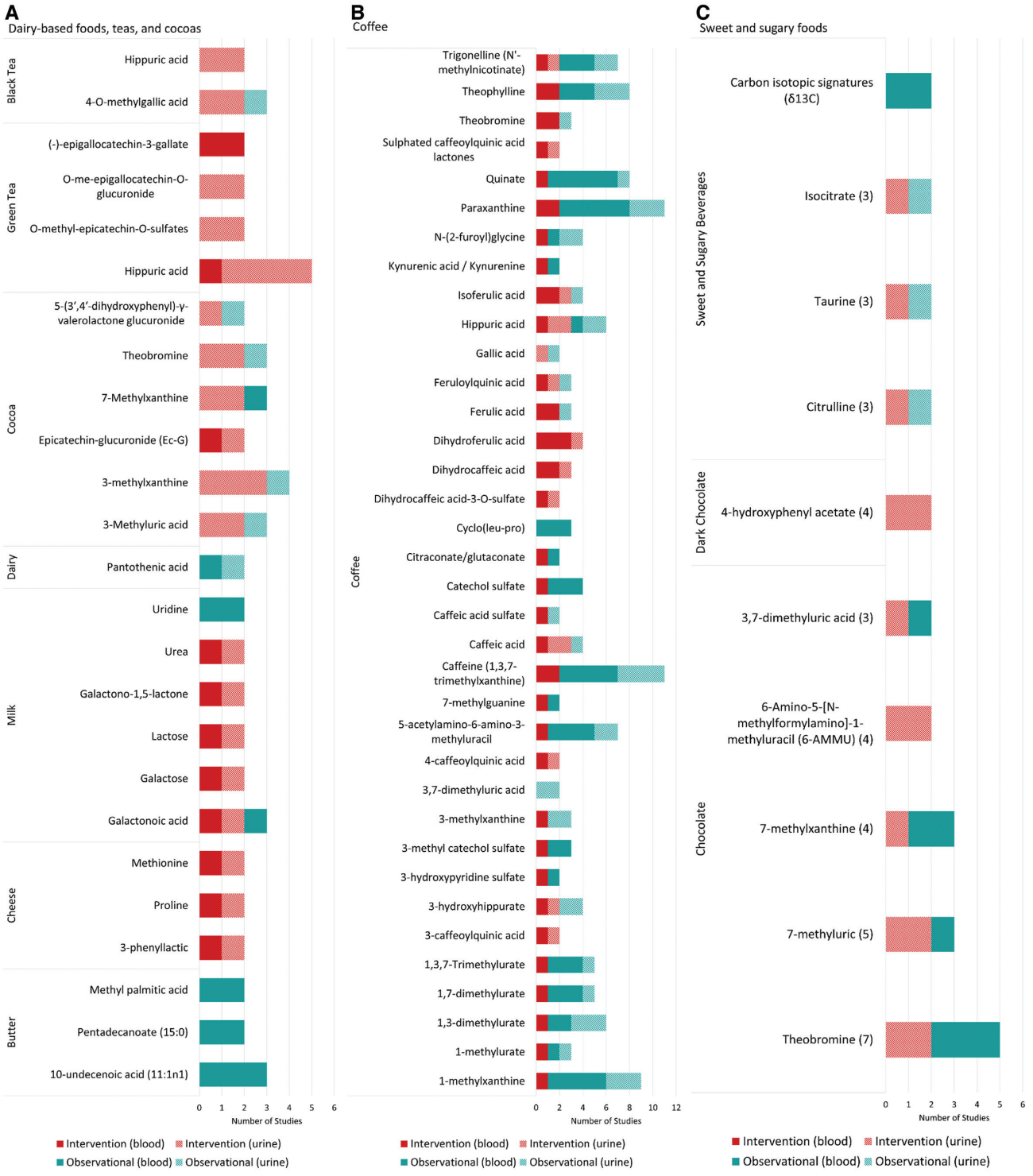

FIGURE 4 Metabolites identified from (A) dairy-based foods, teas, cocoas, (B) coffee, and (C) sweet and sugary foods by number of studies, type of study design, and type of biofluid.

8 observational studies (28, 30, 76, 108, 133, 168, 176, 211), whey in 3 interventional studies (97, 185, 212), soy-based drink in 3 interventional (178, 182, 183) and 2 observational studies (31, 34), high-soy diet in 2 interventional (213, 214) and 5 observational studies (23, 76, 215–217), and soy-based cheese in 1 interventional (urine and plasma) study (218). Elevated levels of theobromine and proline betaine were reported for ADD (33, 194); β-cryptoxanthin for DASH diet (108, 197); TMAO (33, 194, 196) and hippuric acid (33, 196) for NND; and CMPF (96, 108), eicosapentaenoic acid

FIGURE 5 Metabolites identified from dietary patterns and other foods by number of studies, type of study design, and type of biofluid. DASH, Dietary Approaches to Stop Hypertension Trial.

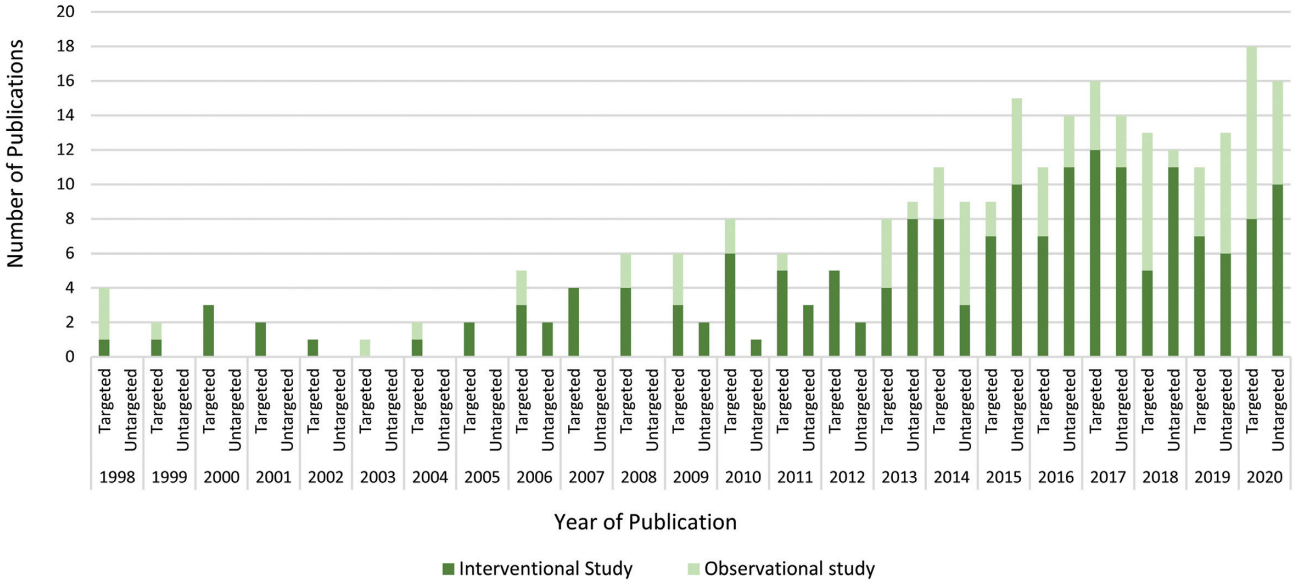

FIGURE 6 Number of publications in nutritional metabolomics. Note: Data presented are based on the inclusion criteria of this review.

(20:5n–3) (96, 108), and hippuric acid (96, 198) for HEI. A higher level of DHA (22:6n–3) was found to be associated with consumption of a Mediterranean diet (26, 108, 199). In addition, a higher concentration of hippuric acid for fruits and vegetables (69, 176, 208), glycine for vegan diet (100, 104, 112), common dietary isoflavones daidzein and genistein for high-soy diet (23, 213–217) and soy-based cheese (218), and pinitol for soy-based drink (182, 183) were identified as the most frequently reported markers.

Discussion

This review included 244 articles (169 interventional studies, of which 9 studies were replicated in free-living participants) that assessed the association between metabolites measured in common biofluids (i.e., urine, serum, or plasma) and intake of individual food or food groups published between 1998 and 2020. Although there has been a relatively long history of studies using a targeted approach to identify dietary biomarkers related to known constituents of food chemistry, the application of untargeted metabolomics only started to gain prominence in the mid-2000s and has greatly expanded in the past 5–10 y (**Figure 6**). In addition, earlier studies were mainly interventional in design, but the number of observational studies has increased since the early 2000s. Given this trend and combined with recent advances in metabolomics, the application of metabolomics in nutritional epidemiology holds substantial promise.

Metabolites associated with foods or food groups

Based on our review, we rated the repeatability of 69 metabolites as good, 161 as fair, and 48 as poor markers of specific foods. Specifically, results from this review indicate that proline betaine for fruits in general, but also for orange, orange juice, and citrus fruit, was the most repeatable (based on interstudy repeatability and study design). In addition, the following have good evidence and were also highly repeatable: pelargonidin glucuronide for strawberry; sulforaphane, sulforaphane cysteinylglycine, sulforaphane *N*-acetylcysteine, and sulforaphane cysteine for broccoli; sulforaphane for broccoli sprouts; alkylresorcinols for high-fiber (grain-rich) foods; creatinine for meat; 3-methylhistidine for chicken/poultry; acetylcarnitine for red meat and processed meat; DHA for seafood in general and fatty fish; TMAO for fish and NND; Σmethyl(epi)catechin glucuronides for red wine; methylgallic sulfate for dealcoholized red wine; 4-*O*-methylgallic acid for black tea; hippuric acid for green tea; 3-methylxanthine for cocoa; paraxanthine and caffeine for coffee; theobromine for chocolate; galactonate for milk; daidzein for high-soy diet; and hippuric acid for fruits and vegetables. This subset of metabolites is consistent with several previous reviews (18, 219–221).

It is important to mention that several other metabolites also had good evidence (i.e., ≥5 points) but were not found to be among the most repeated markers (i.e., not with the most points within the good category) (Table 1). For example, DHPPA for high-fiber (grain-rich) foods appeared in 2 interventional studies (score: 2 × 2) and 1 observational study (score: 1 × 1), and we can classify this to be of good evidence (i.e., score ≥5) (Table 1, Figure 2B). However, because alkylresorcinols appeared in 4 interventional studies (score = 8) for the same food group, it was considered to be the "best" candidate metabolite (i.e., highest score).

Study designs

All articles included in this review identified metabolites in human samples, and ∼70% of the studies included were interventional in design (>50% of studies used a crossover design). Of the 69 metabolites with good evidence, 48 were

reported in both interventional and observational studies, 20 were found only in interventional studies, and 1 was found only in observational studies. A crossover design is ideal for assessing metabolites because participants act as their own control, which lowers variability due to physiological variation between individuals, lifestyle factors, and reporting bias (222). Most of the included interventional studies reflect short- to medium-term effects of diet or focus on a single food (e.g., orange juice) or food group (e.g., meats), whereas observational studies can be more informative because most have a large sample size (on average, 42 and 922 participants per interventional and observational study, respectively) and focus on multiple foods and/or food groups simultaneously. However, understanding the potential for biomarkers in observational designs is important because they are most likely to suffer from biases due to misreporting. Although we identified several markers in both study designs, there were a few markers that have not yet been identified in observational designs, likely due to lack of observational studies examining these biomarkers. For example, although our review proposed isothiocyanates as a candidate dietary biomarker for broccoli consumption, they have yet to be examined in observational studies to assess their robustness (223). However, we are confident that isothiocyanates may serve as a quantitative measure of short-term broccoli consumption because this biomarker was not associated with any other commonly consumed food. In contrast, we are less confident in a biomarker representing a particular food if that marker is yet to be identified in a free-living population and is not specific to a food (e.g., hippuric acid, a candidate marker for green tea, is also shown to be a candidate marker for fruits in general, fruits and vegetable, and coffee). In comparison, 3-methylhistidine as a biomarker for chicken/poultry consumption might serve as a valid marker for both short- and long-term intake because it was shown in both interventional and observational studies, with the conclusion that both study designs will provide important and unique information necessary to advance dietary biomarkers research (224).

Metabolomic approaches

Of the 69 metabolites with good evidence, 38 were identified using both untargeted and targeted approaches. Some metabolites with good evidence were reported using only an untargeted approach ($n = 9$), whereas others were reported using only a targeted approach ($n = 22$) that benefits from the use of validated assays for their quantitative analysis. Although informative, a drawback of targeted analysis is that it aims to quantify an a priori known subset of metabolites that are usually of related chemical structure and/or biological activity, and therefore discovery of novel markers cannot be achieved (8, 225). An untargeted approach provides the broadest metabolite coverage despite lengthy and complex post-analytical procedures for data filtering and unknown identification that are prone to bias or incomplete structural elucidation if not confirmed by mass spectral comparison and coelution using an authentic standard. Nonetheless, there are potentially yet to be discovered metabolites that may be better indicators for some food groups. For these reasons, whenever possible, both approaches should be applied.

Analytical techniques

All but 1 metabolite with good evidence (DHPPA for high-fiber foods—using HPLC without MS) were identified using LC-MS, 37 were identified using GC-MS, and 17 were identified using ^{1}H-NMR. Likely due to costs, volume requirements, and throughput constraints, less than one-fifth of studies in this review employed cross-platform metabolomic analysis. Moreover, due to the complexity of the metabolome, it is not possible to analyze every metabolite present in a biological sample using $\geq$1 analytical techniques due to their wide dynamic range in concentration and diverse physiochemical properties. In addition, many metabolites are derived from specific foods infrequently consumed in a population or present at low concentrations below detection limits, resulting in missing value inputs. For this reason, it is often necessary to perform sample workup procedures prior to analysis, such as solvent extractions for sample enrichment or background matrix cleanup, noting that a nonselective solvent for sample preparation is preferred for untargeted approaches, whereas targeted approaches sometimes rely on sample preparation procedures optimized for specific chemical groups (226). The results of this review showed that more than half of the food-specific metabolites with good evidence were reported using $\geq$2 independent analytical platforms with acceptable mutual agreement (bias $<$10%) in measured concentrations, such as urinary iodide (227).

Concordance between biological samples

A greater number of studies in this review were based on the analysis of blood (plasma or serum) than urine sample. Notwithstanding that 59 of the 69 food metabolites with good evidence were replicated in both blood and urine sample, DHA for seafood and fatty fish and catechol sulfate for coffee were detected only in blood, and dimethylamine for fish, pelargonidin glucuronide for strawberry intake, hippuric acid for fruits and vegetables intake, and all four metabolites for cocoa intake were detected only in urine. The answer to the critical question of which biological sample (urine or blood) best characterizes intake of these foods thus remains unclear, with some evidence suggesting urine to be the superior biological sample to study nutrient intake or to identify BFIs (8).

Understanding discordance between biological samples

Although few studies in this review that had used both blood and urine samples identified the same metabolites in both biospecimens (42% of the metabolites with good evidence) such as acetylcarnitine for red meat, other studies using both samples did not always find similar results. Typically, urine samples contain a wider variety of exogenous metabolites than blood, which may be phytochemicals, xenobiotics, or chemical byproducts of cooking (8). The nonnutrient

compounds derived from food intake are converted into more polar metabolites to decrease their renal threshold and are thus readily excreted in urine (228). This may explain why fewer metabolites are more likely to be found in blood—blood carries many more nonpolar lipids than urine. Urine is a noninvasive biofluid and less expensive and easier to collect in repeat measures and large-scale studies (especially children) than blood for better adherence. In addition, it reflects a wider range of dietary biomarkers and time window to assess recent food exposures, so it is often considered the preferred sample for identification of food metabolites (22).

The biological variance of metabolites in urine is generally much greater than in blood and requires adjustment for hydration status (e.g., creatinine, osmolality, and specific gravity) when relying on single-point/random collections. In contrast, 24-h urine sampling is ideal for better assessment of average food exposures in observational or nutritional intervention trials, such as DASH-style diets (46), but it is more difficult to collect consistently in large populations. Furthermore, excretion site can influence detection of metabolites. An example of this is the detection of catechol sulfate after coffee intake in blood but not in urine. Catechol, a derivative of coffee processing, is conjugated to catechol sulfate in plasma to facilitate absorption and is generally eliminated in feces (229).

Finally, it is important to consider the time period during which the biological sample is collected and the storage condition of the sample. Most food-specific metabolites are present in human blood and urine for ∼5–10 h, with some extending to 48 h (230). Again, whenever possible, it is recommended to use a 24- to 48-h model in which multiple biological samples are collected and integrated over this longer time period to examine change in metabolite concentration over time or to obtain an average value to represent "true" concentration. Typically, metabolite concentrations change rapidly in blood relative to urine biofluid, so the use of nonfasting sample adds heterogeneity to the results, but some biomarkers are best measured postprandially. In addition, another potential influencing factor in metabolomics may be introduced with improper storage conditions (i.e., temperature, light, or duration), which may possibly lead to metabolite degradation or oxidation such as in the case of PUFAs. There are also concerns of chemical stability if urine samples are not frozen promptly, and thus they require the use of preserving agents such as sodium azide or boric acid to prevent bacterial growth (231).

Strengths and limitations

A major strength of this review is that it provides a detailed and concise summary of all nutritional metabolomic studies reporting metabolites associated with individual foods and food groups that were conducted in healthy participants. We also provided a set of objective, transparent criteria for evaluating repeatability.

However, this review has a few limitations. First, we focused only on blood or urine metabolites and excluded studies using other less common biological samples, such as adipose tissue, feces, breath condensates, and saliva. Second, we were unable to conduct a quantitative analysis due to the variability in metabolite targets and approaches among studies, which makes it challenging to directly compare metabolite concentrations across studies. In addition, the variability in the portion size of foods and/or frequency of food intake (e.g., once compared with repeated) can impose an important limitation when aiming to synthesize and integrate results from individual studies. Third, because the purpose of the review was to rate the evidence of biomarkers based on repeatability, other validation criteria (e.g., specificity) were not assessed in this review (223). Fourth, urine and plasma measured within the same study were each counted as separate investigations and given equal weight because the samples were collected independently with the added advantage for researchers to evaluate whether either specimen could be used due to sample availability. For instance, 3-methylhistidine and proline betaine were consistently demonstrated as robust dietary biomarkers of a prudent diet in both single-spot urine and fasting plasma samples collected from the same participants, which were also associated with self-reported intake of protein and citrus fruit, respectively (12). However, this may have inflated the score for some of the biomarkers. Although we strived toward a reasonable, accurate yet simple score, the score may be biased by the biomarker's physicochemical properties (e.g., detection and concentration, where lower nanomolar–picomolar metabolites or less readily ionizable compounds are less likely to be detected and thus identified). Finally, only a limited number of laboratories have investigated biomarkers associated with food intake; therefore, we were unable to examine interlaboratory variability as required for nutritional epidemiology.

Conclusions

This review has examined and summarized metabolites associated with all possible food and food groups. The results show that although many metabolites can be identified from a specific food, there are many cases in which a single metabolite is a good indicator of food intake. Findings obtained from this review have important public health implications. Dietary advice is an important component of chronic disease prevention and management. Identifying good metabolites associated with food intake in generally healthy populations is an integral step toward examining diet as a risk factor for chronic disease more objectively (232). We recommend that future studies validate these metabolites by using criteria developed by Dragsted and colleagues (223) that include biological plausibility, dose–response, time–response, robustness, reliability, stability, analytical performance, and interlaboratory reproducibility to further advance the use of BFIs in nutritional research.

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